Oslo University Hospital

UiO : University of Oslo

Norwegian PSC Research Center

ANNUAL REPORT 2019

NOPSC

Visit the NoPSC web pages: *www.ous-research.no/nopsc and www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/*

Norwegian Primary Sclerosing Cholangitis Research Center (NoPSC)

ANNUAL REPORT 2019

What is PSC?

Primary sclerosing cholangitis (PSC) belongs to the group of autoimmune liver diseases.

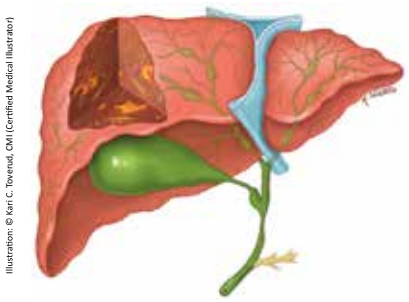
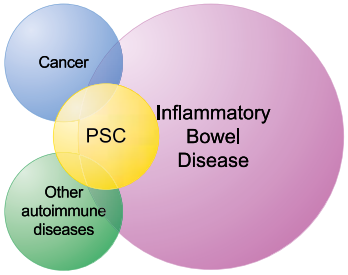


Illustration: © Kari C. Tovenad, CMI (Certified Medical Illustrator)

PSC is a chronic inflammatory disorder that leads to progressive strictures of the bile ducts and ultimately to liver cirrhosis.

There is an increased risk of cancer of both the bile ducts (160-1500x) and the large bowel (5x). PSC is more common in Northern Europe, where approximately 1:10.000 individuals are affected. There is no effective medical treatment available, and PSC is one of the most common indications for liver transplantation in Scandinavia.

Affected individuals are typically young (30-40 years old) and have concurrent inflammatory bowel disease (IBD) in 60-80% of the cases. Disease course is highly variable from patient to patient, but the median time from diagnosis to liver transplantation is 10-15 years.



Primary Sclerosing Cholangitis (PSC) is a patchwork of different phenotypes in addition to the bile duct affection. Most important are inflammatory bowel disease (IBD), malignancy and other autoimmune diseases.

NOPSC Norwegian PSC Research Center

Content:

NOPSC ANNUAL REPORT 2019

More information at the web pages:
www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/
FRONT PAGE: *ScandPSC annual report and the two participating centers; Haraldsplass Deaconess Hospital, Bergen, Norway and Karolinska University Hospital, Huddinge, Sweden*
ILLUSTRATIVE PHOTOS: *Øystein Horgmo UiO*
EDITORS: Tom Hemming Karlsen and Merete Tysdahl
PUBLISHER: Oslo University Hospital
PRINT: Møklegaard Print Shop AS, 2020
SAMPLES: 220

On behalf of the Leadership,
Professor
Tom Hemming Karlsen
Head of NoPSC

Leader´s Corner

The year 2019 was another «stable» year for the Norwegian PSC research center. Activities were running smoothly, thanks to a well-implemented and robust group structure and the support functions of technical and administrative staff. The funding situation was also stable, with an approximate mixture of 25% baseline support from Canica A/S and the rest of the funds covered through external, competitive grants. It has not been, and is still not, within the plans of the center to expand further, rather to continue working within the framework of the current organization.

Two big projects were published in 2019 (see publication list). They both represent the philosophy that we have been fortunate to nurture – that projects are "done when done", each of them representing 8-9 years of effort. The work from group leader Espen Melum on NKT cells reactivity was initiated during his post doctoral stay in Boston from 2010-2012 at the Brigham and Women's Hospital / Harvard Medical School, and later completed in the NoPSC laboratories in Oslo. The work from post doc Georg Schneditz on GPR35 was started on the basis of genetic findings made in 2011-2012. They both illustrate the importance of long-term, stable project financing to make big accomplishments – which NoPSC has been secured by the philanthropic basis of our organization.
A key momentum in 2019 for NoPSC to achieve our aims, was the new collaboration with the US based Halloran Family Foundation. Thanks to an additional philanthropic donation of almost 1.5 mill USD spread across 5 years, we will be able to build, in close collaboration with our Swedish collaborators and counterparts at Karolinska in Stockholm, a registry and biobank-oriented research network throughout other hospitals in Norway and Sweden. The longitudinal study of biomarkers and disease progression that this undertaking allows, will provide crucial information on the natural history of PSC and knowledge that will help us measure the effect of drugs in future clinical trials. The efforts are closely linked with international efforts, particularly at the Mayo Clinic in Rochester, and further in the framework of the International PSC Study Group.

We are still striving to improve further. On the basis of input from our Scientific Advisory Board in June 2019, there is an ongoing effort to enhance the internal collaboration between the groups. The setup is quite extraordinary, representing a comprehensive and complete, translational research facility – all the way from basic science to clinical implementation. The latter also represents a key objective for the current 10 year period of the center. We want to ambitiously translate the knowledge base we have currently generated into clinical applications, and to participate in as many clinical trials as possible – complementing the work of the clinical research groups on biomarkers and disease behavior (cholangiocarcinoma development included).

The circumstances of our research activities are less certain. The building plans for the new Oslo University Hospital Campus are evolving and likely means a shift from the current localization into new facilities. The close link between clinical patient management and the translational research at NoPSC and the Department of Gastroenterology, which is a key element to our success, is challenged under these circumstances, and the situation raises questions on what is the ideal organization of translational research activities versus clinical routine. We will not be the ones to have the final word, and hope that our framework units, the Research Institute of Internal Medicine and Department of Transplantation Medicine, will take the right decisions to secure the future of research units like ours during the years of change to come.

I would end my words of this year's annual report by thanking all our staff for their hard work and the spirit that they bring to our team. I believe we have an enthusiastic and friendly working environment that in the end is a key part of the formula that allows us to keep working like we do.

Overview of the Norwegian PSC Research Center

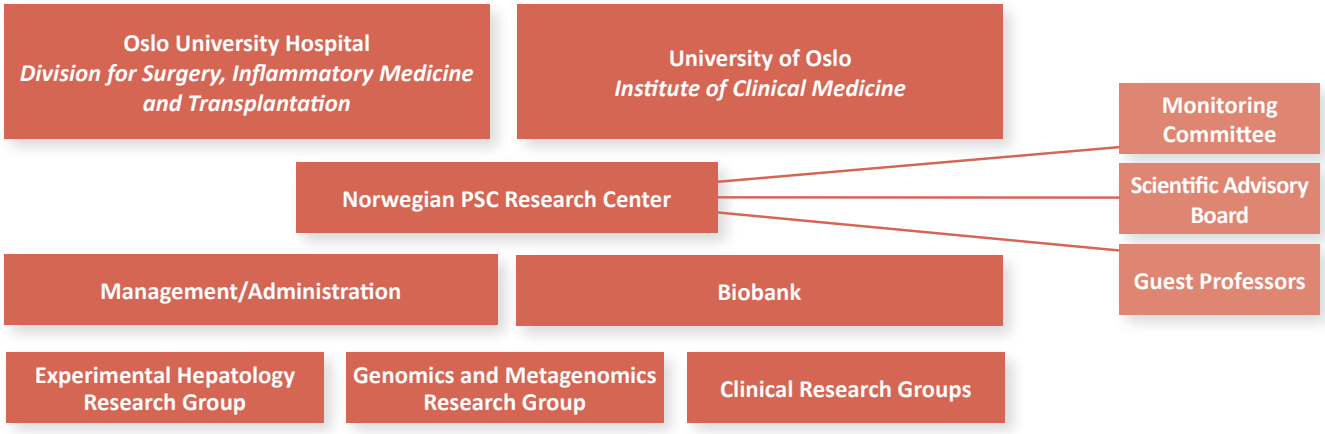
NoPSC was established May 2008 at the Medical Department, Rikshospitalet, upon signing the contract between the University of Oslo and Rikshospitalet on the handling of funds from Canica A/S. The basis of this agreement was a donation from Stein Erik Hagen of NOK 100 millions made in September 2007 to substantially strengthen research related to basic and clinical aspects of the chronic liver disease Primary Sclerosing Cholangitis. From 2017 Canica A/S has provided another NOK 50 millions for a new ten-year period based on a contractual agreement between Canica A/S, Oslo University Hospital and the University of Oslo as of December 2014.

Aims of the PSC Research Center

- Ensure targeted and prudent management of the private donation
- Motivate high-quality PSC research in Norway
- Coordinate and distribute resources for PSC research in Norway
- Establish international collaborations when needed
- Establish and run Biobank and PSC Registry

ORGANIZATION

NoPSC has status as a center at the Medical Faculty, Institute of Clinical Medicine University of Oslo and is organized within Oslo University Hospital as a section (level 4 unit) within the Department of Transplantation Medicine at the Division for Surgery, Inflammatory Medicine and Transplantation. The Experimental Hepatology Group and the Genomic and metagenomics group are organized at the Research Institute of Internal Medicine, Oslo University Hospital, while the clinical groups are organized within the Section for Gastroenterology and Hepatology at the Department of Transplantation Medicine, Oslo University Hospital and Haraldsplass Deaconess Hospital, Bergen.



MONITORING BOARD

The Board monitors that the Center is managed according to the Aims. Next year's budget is discussed in the autumn while the Annual report and the accounting are reviewed at the spring/summer meeting. The center´s scientific activities are also presented at the monitoring board meetings.

LEADER
Prof. Dag Kvale,
Head of the institute of Clinical Medicine, University of Oslo

Hans Mossin
Adm. Head of the *Institute of Clinical Medicine, University of Oslo*

Nina Paulsen
Canica A/S

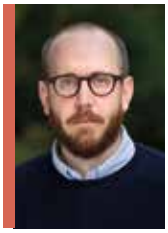
Daniel Sørli
Canica A/S

Dr. Morten Tandberg Eriksen, *Head of Div. of Surgery, Inflammatory Medicine and Transplantation, OUH Rikshospitalet*

Prof. Bente Halvorsen,
Research Institute of Internal Medicine, OUH Rikshospitalet

Prof. Tom Hemming Karlsen,
Center leader, is also part of the monitoring board.

GUEST PROFESSORS



Ass. Prof. Niklas Björkström
Unit of Gastroenterology and Rheumatology, Karolinska University Hospital, Huddinge, Sweden

Prof. Massimo Pinzani,
Institute of Immunity & Transplantation Royal Free Hospital, London, UK

SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Board (SAB) was formally established in 2015 and reviews the center biannually.

Prof. Herbert Tilg
University of Innsbruck, Austria

Prof. Terje Espevik
University of Science and Technology (NTNU), Trondheim, Norway

Prof. Tore Kvien
University of Oslo, Norway

MANAGEMENT

The management has the overall responsibility for the day-to-day work performed at the Center.

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Researcher Dr. Trine Folseraas
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Merete Tysdahl
Administrative coordinator.
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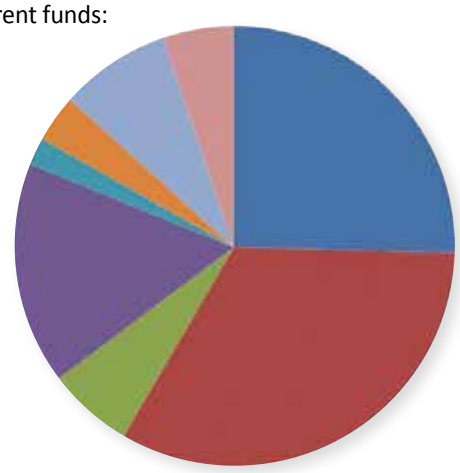
ACCOUNTING

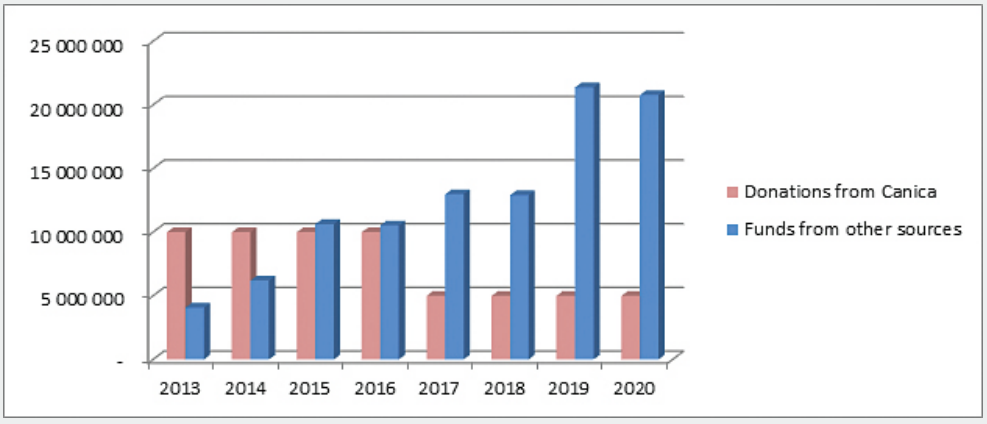
In 2019 the total amount of expenditures within the Center was 22,337 mill NOK. 7,087 mill NOK were from Canica funding, and out of these 5,670 mill NOK were from the Canica donation and 1,417 mill NOK were gift reinforcement provided by the Norwegian Research Council. The remaining 15,250 mill NOK expenses in 2019 were covered by independent grants (also including additional funds from the Norwegian Research Council). This shows that the Canica donation now covers about 25% of our total expenditures. This development is in accordance with our goal to keep increasing the external fraction of the overall Center funding.

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	**EXPENSES**	**INCOME**	**EXPENSES**
TRANSFER FROM 2018	431 980			
INTEREST				
OTHER INCOME	183 135			
TRANSFER FROM UiO	4 441 281			
WAGES		3 040 070		4 441 281
OVERHEAD		360 962		940 988
INFRASTRUCTURE		114 410		138 148
OTHER OPERATING EXPENCES		2 366 066		126 367
TRANFER TO 2020		**- 825 112**		**9 667 530**

	2019
Canica	5 670
S-E Norway Regional Health Authorithy	7 375
Gift reinforcement NRC	1 417
Norwegian Research Council	3 675
University of Oslo	449
EU funds (Dynaflow)	780
ERC grant	1 816
Satsningsmidler OUS	1 155
Thousand NOK	**22 337**

This pie chart shows the expenditure distribution between the different funds:





Awards

Beate Vestad, PhD student in the Genomics and Metagenomics group of NoPSC won the Tore Midtvedt Prize for her abstract "Interplay of Gut Microbiota and Immunodeficiency on Excess Metabolic Risk in HIV Infection", at the National Microbiota Conference 19th of November 2019 in Oslo.

Marit Mæhle Grimsrud recieved a prize for her work on «Epigenetiske biomarkørar i galle dentifiserer kolangiokarsinom hos pasientar med primær skleroserande kolangitt med høg diagnostisk nøyaktigheit» at Norwegian Gastroenterology Society's annual meeting at Lillehammer 7-9th of February 2019.

NEW GUEST PROFESSOR AT OUR CENTER IN 2019

Fotograf: Markus Marcetic

Massimo Pinzani is Professor of Medicine and Sheila Sherlock Chair of Hepatology at University College London, Institute for Liver and Digestive Health, Division of Medicine, based at the Royal Free Hospital in London, UK. He is one of the pioneer researchers in the area of liver fibrosis providing seminal contributions to the knowledge of the cellular and molecular mechanisms and to the relative clinical applications. Current research is centred on regenerative medicine and in particular on the development of extracellular matrix scaffold of liver, pancreas and small intestine for cell bioengineering and 3D disease modelling. Professor Pinzani`s research activity is summarised in more than 250 original peer-reviewed publications (H Index of 91, Scopus). He has served in the governing and scientific boards of major international organization in the area of Hepatology and Gastroenterology, and as Editor in Chief and Associate Editor of top peer reviewed international journals in the area of Gastroenterology and Hepatology. He has also served as Educational Chair and member of the governing board of the European Association for the Study of the Liver (EASL). Professor Pinzani is a Fellow of the Royal College of Physicians (London) (FRCP) and of the American Association for the Study of Liver Diseases (FAASLD).

Strategic Prospective Scandinavian PSC Biobank (ScandPSC)

PROJECT BACKGROUND AND AIMS

Strategic Prospective Scandinavian PSC Biobank (ScandPSC) merges two strong scientific environments in Norway and Sweden with well-established PSC biobanks and more than 30 years of legacy in a collaborate effort to collect a large prospective biological and clinical sample collection. Scandinavia is a geographical "hot-spot" for PSC, with a high willingness in patients to participate in research studies and very good healthcare infrastructures coupled to unique national registries, altogether providing ideal conditions for high-quality, well-powered prospective studies.

Our aim is to establish the world's largest prospective PSC biobank and registry, as a platform for clinical trials and biomarker discovery, with 1300 patients enrolled per 2023.

PROJECT STATUS 2019

Building the organization and infrastructure of the project have been major tasks for the Management Group in 2019 since funding was granted from the Halloran foundation in August. A full Project Protocol and Standard Operating Procedures (SOP) for biological sampling, processing and storage have been developed, and a Collaborations Agreement between Oslo, Bergen and Stockholm has been signed. Collaboration agreements are established with all hospitals in the South-East and West Health Regions in Norway and with all 7 university hospitals in Sweden. Ethical approval for data registry and a study specific biobank is granted in Norway and the application for ethical approval is submitted in Sweden. The common study biobank is physically centralized to the fully automated Biobank Haukeland in Bergen for Norway and to a study specific ultra-freezer at Karolinska University Hospital for Sweden, with biobank material transfer from participating centers at regular intervals.

Receiving stocks was a challenge for Oslo University hospital. Finally, at the end of 2019 the systems were set up to receive the stocks and release the funds. Mette Vesterhus is currently employed as project coordinator in Norway while applicants are being evaluated; in Sweden, research nurse Marta Stenberg will start in the position as national coordinator April 1st 2020.

Patient inclusion is according to plan. Publication of a patient information folder is pending. In Norway, the NoPSC prospective cohort existing since 2013 (3 centers: Bergen, Rikshospitalet and Ahus) constitutes the basis from which of the ScandPSC biobank will spring. In total, the prospective cohort includes 196 PSC patients, with biobank serum samples. In Sweden, the project was started at Karolinska Institute in 2019 and 70 patients were included in the project using temporary paper CRFs. Blood, plasma and serum samples were collected and stored temporarily in the existing facilities at Karolinska Institutet & Karolinska University Hospital, constituting the foundation of the novel biobank.

DATABASE AND E-CRF

The variables in the database have been carefully selected and harmonized between Norway and Sweden and, importantly, with the International PSC Study Group (IPSCSG) initiative for collection of clinical variables, which opens for future global collaboration. An e-CRF for clinical data retrieval has been developed and piloted in Norway, using a well-established platform operated by VieDoc which is approved by and accessible in all Norwegian health regions, whereas in Sweden, a similar eCRF is being developed.

BIOBANK MATERIAL AND IMAGING

Serum samples will be collected from all patients at baseline and annual follow-up. Full blood for DNA extraction will be collected at baseline from all patients. Faecal samples and saliva will be collected from all patients at least once. MRI (MRCP and/or contrast MRI of the liver) will be acquired at annual intervals. Ultrasound elastography (Fibroscan or other) will be performed annually at centers where this is available.

NETWORK EXPANSION PLAN

In Norway, we plan recruitment of 7 new centers in 2020 primarily in the South-East Health Region. Furthermore, additional patients will be recruited in the existing centers; Bergen, Rikshospitalet and Ahus. In Sweden, recruitment of new patients is planned at Karolinska Institutet & Karolinska University Hospital throughout 2020. All 7 university hospitals in Sweden plan to start data collection and biobanking in the fall of 2020, provided ethical approvals are achieved. Additional centers outside of the university hospitals are also invited. Patient inclusion is expected to expand gradually during 2021 in both Norway and Sweden.

ScandPSC meeting in Oslo, January 2020. From left; Annika Bergström, Trine Folseraas, Johannes Hov and Mette Vesterhus.

MANAGEMENT GROUP (LEADERSHIP TEAM)

Mette Vesterhus, Associate Professor, MD, PhD
Haraldsplass Deaconess Hospital, Bergen, Norway

Annika Bergquist, Professor, MD, PhD
Karolinska University Hospital, Huddinge, Sweden

Tom Hemming Karlsen, Professor, MD, PhD
Oslo University Hospital, Norway

Niklas Björkström, Associate Professor, MD, PhD
Karolinska University Hospital, Huddinge, Sweden

EMPLOYED PROJECT COORDINATORS

Marta Stenberg, Study Nurse, Sweden

STEERING COMMITTEE

National PI Annika Bergquist (Sweden) and Mette Vesterhus (Norway), and lead physicians from collaborating centers (CI) in Norway and Sweden.

FUNDING

The project is funded by a generous donation from the Halloran family foundation.

MONITORING BOARD

The Monitoring Board of the Norwegian PSC Research Center (NoPSC) will oversee the management of the funds.

Project portfolio // Research groups

CLINICAL RESEARCH GROUP, BERGEN

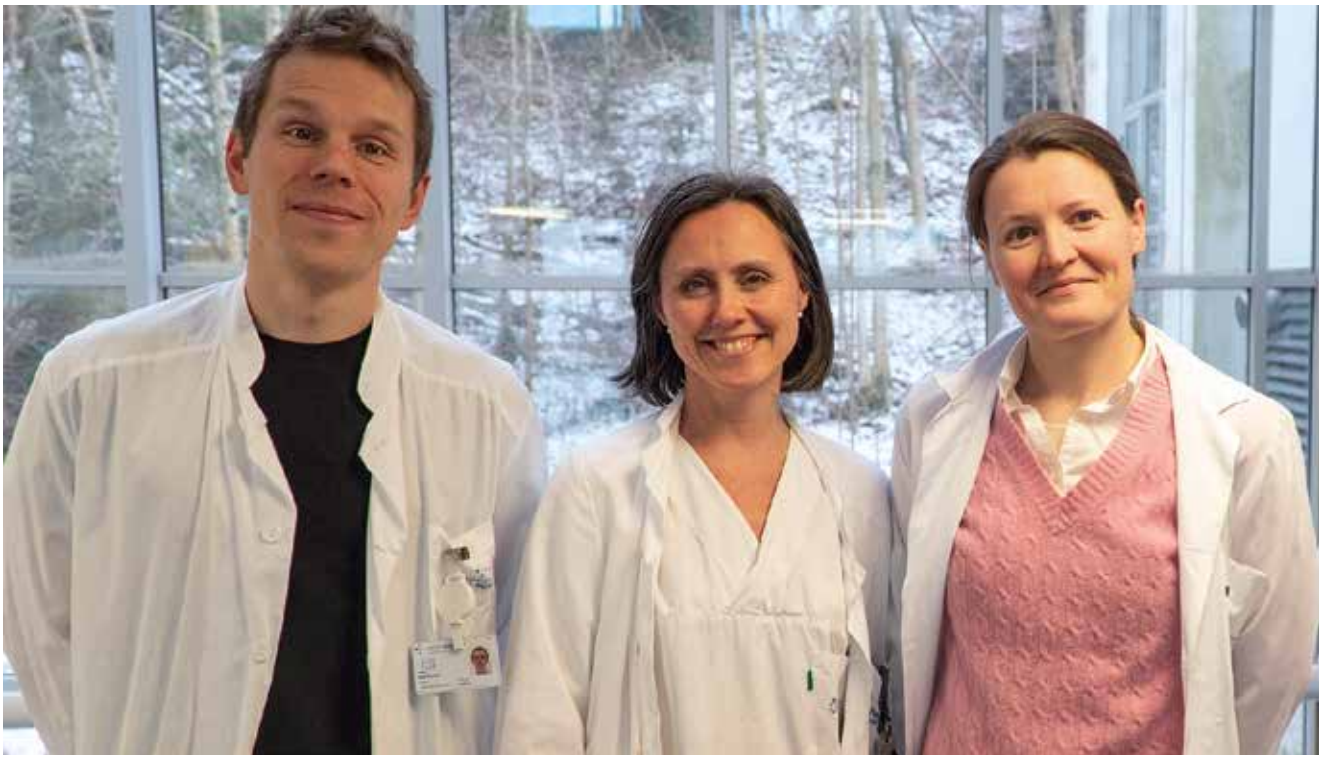


Photo: Private

From left: Anders B. Mjelle, Mette Vesterhus and Guri Fossdal.

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RESEARCH PROFILE

The main focus of the Clinical Research group in Bergen is the identification, evaluation and establishment of prognostic biomarkers and surrogate markers of disease activity and severity in PSC. We collaborate closely with the Metagenomics and Clinical groups in Oslo. The establishment of biomarkers to predict clinical outcome is highly warranted to allow for personalized follow-up based on risk stratification and to facilitate the development of effective treatment through improved patient selection and assessment of treatment effect.

BIOMARKERS OF DISEASE ACTIVITY AND PROGNOSIS IN PSC

We were the first to identify and validate, in an international multicenter panel, the ELF®Test as an independent prognostic marker in PSC in 2015 and 2017, respectively. While later confirmed by others, prospective validation is pending. Currently, the analysis is being evaluated at one laboratory in Norway but is available for research

only. In collaboration with corporate partner Nordic Biosciences in Denmark and the Royal Free Hospital (London, UK), we have explored novel, more specific and dynamic biomarkers of fibrosis in PSC, interestingly revealing differences compared to other autoimmune liver diseases. We now want to explore a broad biomarker panel reflecting several of the suggested disease pathways, aiming to define a model better capturing disease risks and outcomes in patients.

IMAGING AND ARTIFICIAL INTELLIGENCE

Artificial intelligence offers exciting new opportunities in biomarker research, particularly in regards to imaging. NoPSC is involved in studies involving artificial intelligence techniques investigating MRI in PSC, primarily through a strategic collaboration with the Mayo Clinic. One paper emerged from this collaboration in 2018 regarding the development of a prognostic clinical scoring system using machine-learning techniques, and further studies are ongoing. We have also contributed to ongoing MRI-related studies initiated through the International PSC Study Group (IPSCSG) and NoPSC will host the annual meeting of the IPSCSG MRI Working Group in 2020.

Liver stiffness measurements using ultrasound elastography has showed promising potential as a prognostic biomarker in PSC. Our group has published reference values for liver stiffness measurements using a range of different platforms for adults (2018) and pediatric populations (2019) which are valuable for the clinical use of liver stiffness measurements in the follow-up of PSC patients. PhD student Anesa Mulabecirovic defended her thesis on liver stiffness measurements (including in PSC) in November 2019. In a current study, we are prospectively evaluating liver stiffness variability and predictive ability.

NATIONAL NETWORK FOR AUTOIMMUNE LIVER DISEASES AND SCANDPSC

We have a major role in the expansion of the NoPSC prospective data and biobank collection initiative, coordinating this effort in close collaboration with the clinical group in Oslo. We spearheaded the establishment of a large local prospective cohort of patients with PSC in 2013, now counting 89 patients, with annual collection of data, imaging and biobanking as well as fecal samples for microbiota studies and patient-reported outcomes. Similar prospective cohorts were initiated at OUH Rikshospitalet (2013) and at Akershus University Hospital (2018). Collectively, the NoPSC prospective cohorts now host 196 patients.

In 2019, we were happy to attract funding from the Halloran Family Foundation to further expand our prospective biobanking initiative into a prospective Scandinavian PSC biobank (described separately). The development of an eCRF for data collection using a web-based platform provided by VieDoc was completed in 2019 and the eCRF was put in production. PhD student Guri Fossdal has fine-tuned the eCRF based on evaluation of a paper pilot and will take care of the practical support and data monitoring as we expect to expand into 7 new centers in the Western and South-Eastern Norwegian health regions in 2020.

CLINICAL TRIALS

It is an important aim for NoPSC to contribute to drug development for PSC through the participation in clinical trials. The prospective cohorts also serve as a recruitment basis for clinical studies. We previously participated in a phase II study for nor-ursodeoxycholic acid and all three centers are currently involved in a phase III clinical trial for the same drug.

KEY COLLABORATORS

- University College London, Institute for Liver and Digestive Health, Royal Free Hospital, UK
- Nordic Biosciences, Denmark
- The Mayo Clinic, Rochester, USA
- International PSC Study Group (IPSCSG)
- Norwegian Centre of Excellence in Gastrointestinal Ultrasonography, Haukeland University Hospital, Bergen

CLINICAL RESEARCH GROUP, OSLO

Photo: Øystein H. Horgmo, University of Oslo

From left: Marit Mæhle Grimsrud, Kirsten Muri Boberg, Lars Aabakken, Liv Wenche Thorbjørnsen, Trine Folseraas, Kristine Wiencke, Merete Tysdahl, Siv Furholm and Vemund Paulsen

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RESEARCH PROFILE

The projects of the clinical PSC research group aim at improving clinical outcomes for PSC patients. Over the last years we have had a particular focus on identification of early detection markers and treatment targets for PSC-associated biliary tract cancer.

MAIN CURRENT RESEARCH THEMES

Identification of early detection markers for PSC-associated biliary tract cancer

We participate in several studies exploring novel markers for early and more accurate detection of biliary tract cancer in PSC. As an example, in collaboration with the Epigenetics

group at the Norwegian Radium Hospital, we have explored the diagnostic utility of DNA methylation biomarkers using bile as liquid biopsy material. More than 300 bile samples from Norway, Sweden and Finland have been analysed in this project. Findings suggest that measurements of aberrant DNA methylation in bile may detect biliary tract cancer at an early stage and show promise to complement current detection methods for biliary tract cancers in PSC.

Molecular characterization and identification of druggable targets in PSC-associated biliary tract cancer
In collaboration with the Department of Pathology at the University Hospital of Heidelberg and the International PSC Study Group (IPSCSG) we have from 2015 onwards collected a large panel of tissue samples from 186 PSC patients with biliary tract cancer from 11 centers in eight countries (Europe and the US). In addition to extensive histomorphological and immunohistochemical characterization, we performed tumor DNA sequencing at 42 known cancer-related genetic loci to detect mutations, translocations and copy number variations. The emphasis made in this project for known cancer-related genes, allowed us to detect many putative therapeutic targets. This opens up for early phase clinical trials of molecular target drugs and personalized cancer treatment in PSC-associated biliary tract cancer. Furthermore, we demonstrated that biliary tract cancer in PSC shows a distinct and homogeneous molecular and morphological phenotype, reminiscent of extrahepatic cholangiocarcinoma. Other projects utilizing this valuable tissue collection is underway.

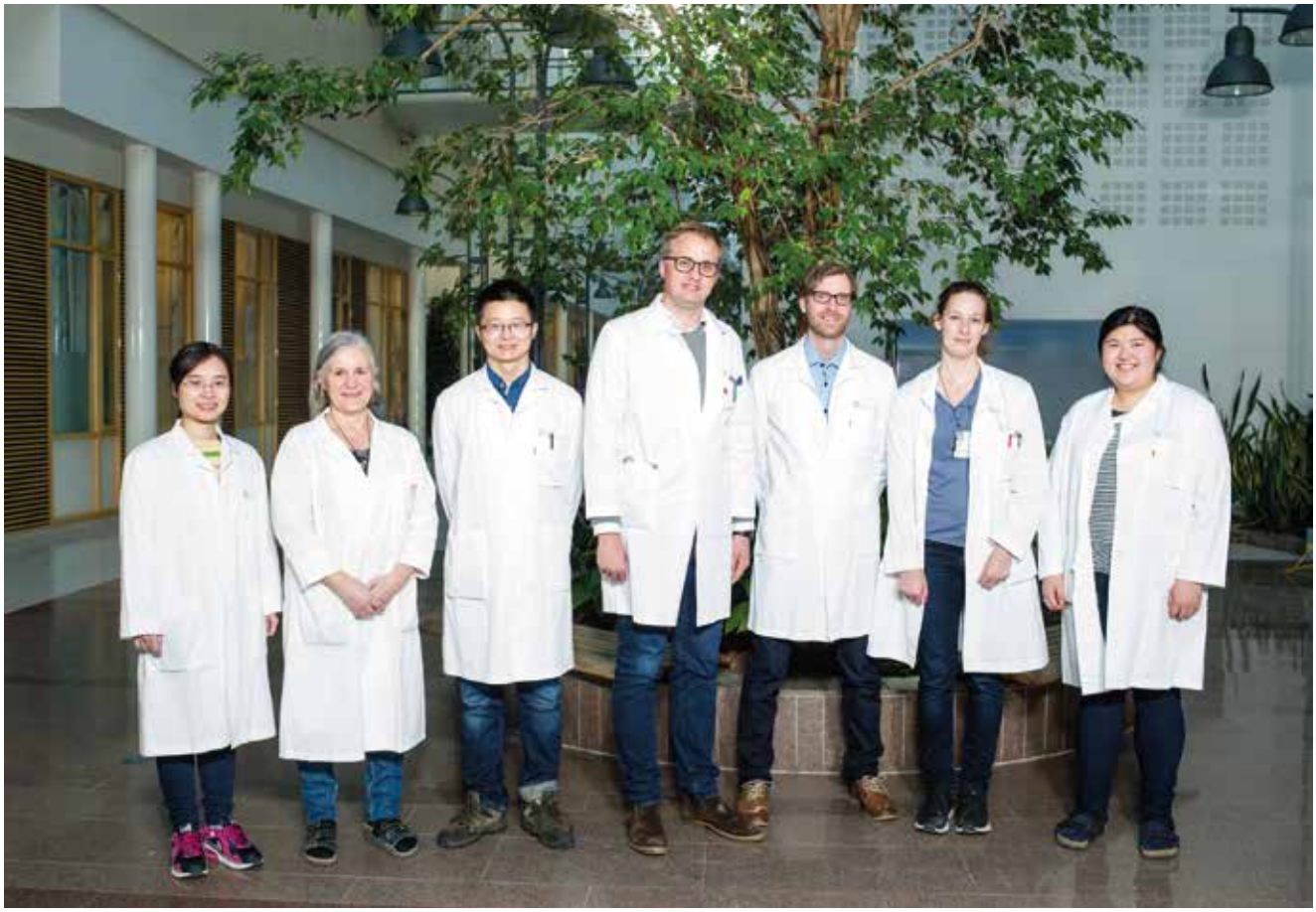
Collaboration within several research networks
Built on the invaluable resource constituted by the Norwegian PSC (NoPSC) clinical registry and biobank (currently including more than 750 PSC patients), we aim to facilitate international PSC research efforts. Previous collaborations within the International PSC Study Group and the IPSC-registry (including more than 450 Norwegian PSC patients) have made it possible to define disease characteristics and factors influencing the disease course across a large number of PSC patients. The registry now contains data from more than 8000 individual patients across 22 countries and 5 continents and enables for research on region specific variation in PSC variables. In 2019 we have contributed extended clinical data on PSC patients with biliary tract cancer to the IPSC-registry to allow for comprehensive retrospective analyses of development, management and outcome of biliary tract cancer in large PSC patient panels.
In addition, as active members of the European Network for the Study of Cholangiocarcinoma (ENSCCA), which currently includes more than 200 investigators from 12 countries, and the COST-action on cholangiocarcinoma (EURO-CHOLANGIO-NET), we have contributed data on PSC patients with cholangiocarcinoma to the ENSCCA patient repository/ database. We will continue the collaboration within these networks and actively participate in research and consensus processes on characterization, management and treatment of PSC and PSC-associated biliary tract cancers.

The NoPSC prospective cohort effort
We contribute actively to the NoPSC prospective cohort and biobank effort by including and following PSC patients locally and by supporting the clinical group in Bergen (which coordinates this effort , see separate section clinical group Bergen).

KEY COLLABORATORS

- The Department of Pathology, Oslo University Hospital, Rikshospitalet.
- The Epigenetics Group at the Department of Cancer Prevention, Institute for Cancer Research, the Norwegian Radium Hospital
- Karolinska University Hospital, Stockholm, Sweden
- The Department of Pathology at the University Hospital of Heidelberg, Germany
- The International PSC Study Group (IPSCSG)
- European Network for the Study of Cholangiocarcinoma (ENSCCA)
- The COST Action CA18122, EURO-CHOLANGIO-NET

EXPERIMENTAL LIVER RESEARCH GROUP



From left: Xiaojun Jiang, Anne Pharo, Fei (Freeman) Zheng, Espen Melum, Jonas Øgård, Katrine Sivertsen Åsrud and Lisa Yuen Løvold

GROUP LEADER

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RESEARCH PROFILE

The experimental liver research group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). The most important tools in our research are mouse models that model aspects of cholangitis development. All of our laboratory activities take place at the Research institute for Internal Medicine.

MAIN RESEARCH THEMES

The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology but also now incorporating aspects of regenerative medicine. In addition to the cholangitis focused studies, we are also doing basic research related to the function of natural killer T-cells, mucosal associated invariant T (MAIT)-cells and other immune subsets. NKT and MAIT cells represents unconventional T-cells that are especially interesting in the context of liver diseases since they are abundantly present in the liver. The ultimate goal of our research is to understand the pathology of and uncover potential novel treatment targets for PSC.

The mouse models we use are immune driven which is in concordance with the leading theories on PSC pathogenesis. In 2019, we continued the hunt for antigens for unconventional T cell antigens in bile and discovered that bile contains antigens for the two major sub-types of unconventional T cells, NKT and MAIT cells. It seems like these antigens are both endogenous and exogenous, and studies are ongoing to determine their molecular identity. As part of the basic studies on the function of NKT cells we published in 2019 that sphingomyelin can block development and activation of NKT cells and affect several disease models. These results were also translatable to the human disease. The team working on unconventional T cells were strengthened in 2019 with Kathrine S. Åsrud who joined as postdoc and will work on the specific role of CD1d on cholangiocytes during bile duct inflammation.

NEW PROJECTS

Tine Simensen Oldereid started as a new PhD student in the group on a collaborative project with Ass. Prof. Henrik Rasmussen at the animal facility using the germ-free unit to study microbiome regulation of bile duct inflammation and development of the immune system. A new line of collaboration with Prof. Stefan Krauss at the center of excellence Hybrid-technology-hub was started up in 2019 where our competence in bile duct biology will be used together with other groups at the hub. In a collaborative project involving a new Scientia Fellow postdoc we also aim to study the bile ducts using organ-on-a-chip systems.

GENOMICS AND METAGENOMICS IN INFLAMMATORY DISEASES

From left to right: Simen Hyll Hansen, Marit Mæhle Grimsrud, Martin Kummen, Alexandra Götz, Georg Schneditz, Lise Katrine Engesæter, Liv Wenche Thorbjørnsen, Brian Chung, Johannes R. Hov, Magnhild Eide Macpherson, Silje Jørgensen and Murat Gainullin

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RESEARCH PROFILE

The projects in the genomics and metagenomics group aim to characterize and understand how alterations in the human genome and the gut microbial flora influence disease. We do this by applying modern genotyping and sequencing technologies, as well as metabolomics.

MAIN RESEARCH THEMES

The main current interest of the group is the role of the gut microbiota in multiple inflammatory disease phenotypes, with a particular focus on primary sclerosing cholangitis (PSC). The main research agendas relevant for PSC are:

Functional microbiomics. Do differences in microbial functions and activity have clinical implications in PSC patients? We aim to delineate functional alterations of the gut microbiome by applying gut microbial profiling or circulating markers of microbial activity (i.e. metabolites) as biomarkers of disease or disease activity and severity.

Recurrent PSC. Recurrence of PSC after liver transplantation is a significant clinical problem, the extent of which is still not fully elucidated. This is a growing priority in the group, being the focus of an ERC Starting Grant and two PhD student projects. The expected outcome of this research axis is both updated epidemiological data, as well as extensive insights into pathogenetic and clinical/ therapeutic aspects of this condition.

Bioinformatics and biostatistics. How can we apply advanced bioinformatics and e.g. artificial intelligence to improve the yield from big data from microbiome or metabolome studies? This is a focus of a new PhD project involving a large cohort of patients with the PSC associated inflammatory bowel diseases.

Post-genetic studies. Could autoimmunity in PSC originate in the gut? We are pursuing this question in the project "Identifying exogenous drivers of autoimmunity in the gut microbiome". In addition, we are also pursuing further studies of GPR35 in the context of inflammatory disease.

Clinical microbiota medicine. Interventions targeting the gut microbiome to treat disease may provide substantial evidence of causal relationships between the gut microbiome and disease. This is a key topic of the Strategic research area at Oslo University Hospital which was awarded to the group in 2019, "*Personalized microbiota therapy in clinical medicine*"

FUNDING

The people in the group were in 2019 funded by one ERC Starting Grant, one grant from the Research Council of Norway (closing 2020), seven PhD or postdoc grants and one network grant from the Regional Health Authorities of South Eastern Norway, in addition to Canica, funding one bioinformatician, and Nordforsk, funding one engineer.

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

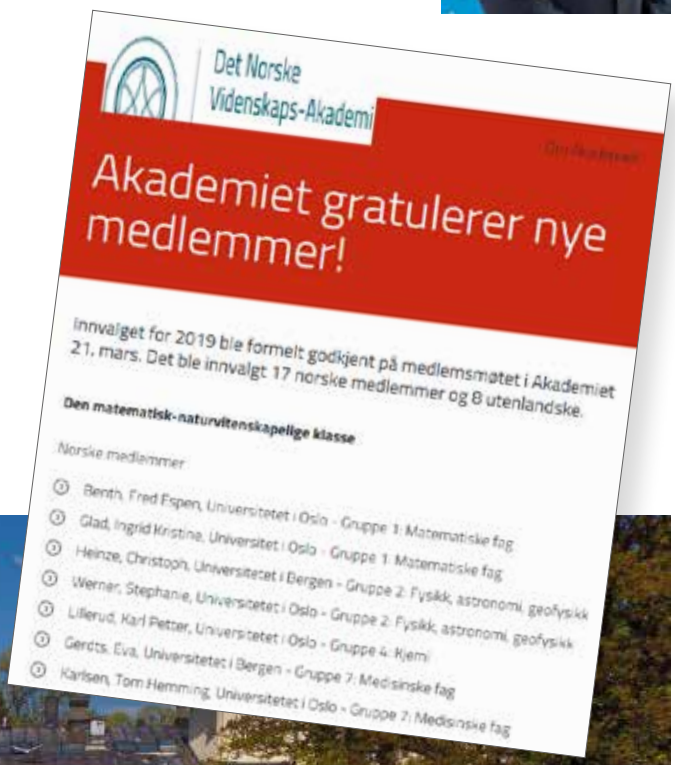
- Locally, the group is closely integrated with the clinical microbiology and microbiota medicine group, it has extensive collaborations ongoing within the Research Institute of Internal Medicine, multiple clinical research groups as well as pathology and radiology. A strong link to the experimental groups is also important, providing opportunities to understand disease mechanisms in more detail.
- Regionally, the group has continued its work with a collaborative research network centered on the meetings in the regional interest group Oslo microbiota forum. This network was formally funded from late 2018 with the name ReMicS (Regional research network for clinical Microbiota Science), with Hanne Guldsten as administrator. In addition, the group hosted the sixth national conference on gut microbiota in November 2019.
- Internationally, we continue multiple strong collaborations both within and outside the International PSC Study Group.

PROFESSOR TOM HEMMING KARLSEN INVITED TO BECOME A MEMBER OF THE NORWEGIAN ACADEMY OF SCIENCE AND LETTERS (DET NORSKE VITENSKAPS-AKADEMIET)

The Norwegian Academy of Science and Letters acts as a national contact body both within and between the individual scientific disciplines, and represents Norwegian science vis-à-vis foreign academies and other international scientific organizations. Since the fall of 2018 the Academy has a representative in Brussels, working to improve the collaboration with EASAC and focusing on the subject of Science Advice. The Academy aims to fulfill its mission by initiating and supporting research, organizing meetings and international conferences, publishing scientific writings and appointing representatives to national and international bodies.

The Academy has approximately 900 Norwegian and foreign members, divided into two sections: Mathematics and Natural Sciences and Humanities and Social Sciences. The sections are then further split into eight groups. Prof. Karlsen was in the spring 2019 invited to join the group of Medical Sciences in the division of Mathematics and Natural Sciences in The Norwegian Academy of Science and Letters.

It is a great acknowledgement to be invited into this prestigious Academy and NoPSC is proud and honored to have Prof. Karlsen as a member there.


Det Norske Videnskaps-Akademi

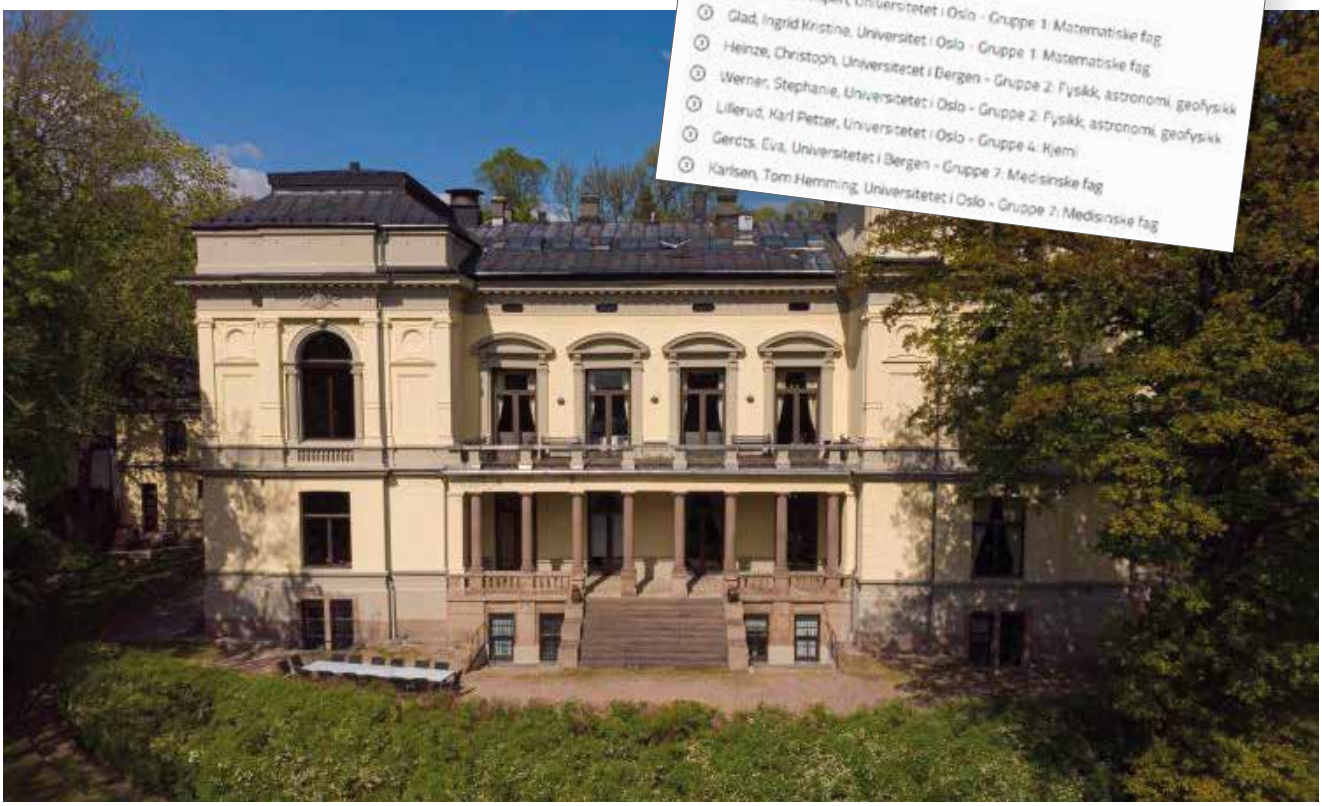
Akademiet gratulerer nye medlemmer!

Innvalget for 2019 ble formelt godkjent på medlemsmøtet i Akademiet 21. mars. Det ble innvalgt 17 norske medlemmer og 8 utenlandske.

Den matematisk-naturvitenskapelige klasse

Norske medlemmer

- Benth, Fred Espen, Universitetet i Oslo - Gruppe 1: Matematiske fag
- Glad, Ingrid Kristine, Universitet i Oslo - Gruppe 1: Matematiske fag
- Heinze, Christoph, Universitetet i Bergen - Gruppe 2: Fysikk, astronomi, geofysikk
- Werner, Stephanie, Universitetet i Oslo - Gruppe 2: Fysikk, astronomi, geofysikk
- Lillerud, Karl Petter, Universitetet i Oslo - Gruppe 4: Kjemi
- Gerdts, Eva, Universitetet i Bergen - Gruppe 7: Medisinske fag
- Karlsen, Tom Hemming, Universitetet i Oslo - Gruppe 7: Medisinske fag

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Highlights 2019

NOPSC RETREAT

NoPSC's annual retreat for 2019 was held at Holmenkollen Park Hotel in January. The main focus of the retreat program was the PSC patient in relation to Cholangiocarcinoma, Liver Immunity and Liver Transplantation. The retreat was also a guest professor meeting, with Dr. Niklas Björkström and Prof. Michael Trauner. The program comprised updates from the research groups and social activities. More than 30 people participated in the event. (1)

NORWEGIAN GASTROENTEROLOGY ASSOCIATION

At the annual meeting for Norwegian Gastroenterology Society at Lillehammer at Lillehammer 7-9th of February 2019, Mette Vesterhus was elected as the leader for the next two years. Also at this meeting Marit Mæhle Grimsrud received a prize.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

Tom H. Karlsen has had the role as Secretary General for the Governing Board of the European Association for the Study of the Liver (EASL) since April 2017, and completed his service there in April 2019. His engagement in international liver research and health care politics through EASL and beyond continues to be of great importance. EASL has also provided possibilities to influence and build contacts both in EU and WHO on important hepatology issues, key research funding programs and regulations.

THE INTERNATIONAL LIVER CONGRESS

EASL arranges an annual International Liver congress, and in 2019 it was held in Vienna, Austria, 10-14th of April. NoPSC was represented with several people. There Prof. Phil Newsome took over the role as Secretary General from Prof. Tom Hemming Karlsen.

RIIM SPRING SEMINAR

The Research Institute for Internal Medicine (RIIM), where NoPSC physically is placed at Oslo University Hospital, arranges each year a spring conference. In 2019 the Spring Conference was held at Forskningsparken 7th of May. This one day event consisted of a scientific program with invited speakers; Einar Martin Aandahl, Jan Terje Andersen and Anna-Maria Hoffmann-Vold, in addition to our own researchers from the institute, social events and dinner. (2)

MONITORING BOARD MEETINGS

In 2019 the first Monitoring Board meeting for NoPSC was the 22dn of August. Here the accounting for 2018 and the annual report was presented. The second Monitoring Board meeting took place on the 5th of December and the budget for 2020 was presented and approved.


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DEBATT OG KRONIKK
Kritikkverdig å fjerne refusjon til alvorlig syke uten varsel
Vi er kritisk til at Helfo – uten varsel – har endret praksis og ikke lenger gir refusjon for annenlinjebehandling til alvorlig syke pasienter som ikke kan bruke standardbehandling. Leger og pasienter fortviler – og vi ønsker gjeninnført en enhetlig nasjonal løsning som gir rett til refusjon for annenlinjebehandling når dette er indisert.

YOUNG RESEARCHER TALENT

Espen Melum received Young Researcher Talent funding from the Norwegian research council for the project "Unconventional T-cells in bile duct inflammation" in 2017. The project started in 2018 with Freeman Fei Zheng engaged as a PhD student, and in 2019 Kathrine Sivertsen Åsrud was engaged for a 3 year position as a postdoc.

SCIENTIFIC ADVISORY BOARD

The NoPSC Scientific Advisory Board had a review of the center in 2019. They provided NoPSC with many useful advice and suggestions. As they also said in their previous report, the SAB is of the opinion that the center is extremely successful and has high visibility in the international community. The scientific output is very good and both UiO and OUH Rikshospitalet can be proud of the center. (2)

ERC FUNDING

In 2018 Johannes Hov at NoPSC was awarded a European Research Council (ERC) Starting Grant of EUR 1,5 million over 5 years to further develop his research on the importance of intestinal bacteria as a cause of disease. The project is called "Stop Autoimmunity - Recurrent disease in the liver transplant: window to identify and stop gut signals driving autoimmunity". The project started in July 2019.

GUEST PROFESSOR MEETINGS

The first guest professor meeting in 2019, where our PhD students and Post docs get valuable feedback on their projects and careers was combined with the annual retreat. The other guest professor meeting 15-16th of October 2019. Dr. Michael Trauner Medical, University of Vienna, Austria, completed his engagement as a guest professor for NoPSC at the retreat in January 2019. Dr. Niklas Björkström from Karolinska Institutet, Huddinge, Sweden, continued through the year and Prof. Massimo Pinzani from Institute of Immunity & Transplantation at Royal Free Hospital, London, UK, graciously accepted our invitation to become our new guest professor, with his first meeting being in October 2019.

PATIENT BOARD

With the ongoing focus on involving patients as active participants in the planning of research projects, we are grateful for the participation from the patient organization (Foreningen for Autoimmune Leversykdommer, FAL) in our annual meeting to discuss our planned research initiatives. Last time was in September 2019.

IN THE MEDIA

Group leader Mette Vesterhus, with others, published a feature story entitled "Kritikkverdig å fjerne refusjon til alvorlig syke uten varsel" in Dagens Medisin 8th of November 2019. (3)

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NEW PROFESSOR

Our group leader Johannes E.R. Hov in the Genomics and Metagenomics group at NoPSC was December 1, 2019 employed as Adjunct professor (professor II) of gastroenterology at the Department of Transplantation Medicine, University of Oslo, in combination with a consultant position at Section of Gastroenterology, Oslo University Hospital. We are very proud of this accomplishment of one of our group leaders.

THE LIVER MEETING

Also this year NoPSC had a delegation at The Liver Meeting, the American Association for the Study of Liver Diseases's annual conference. This time in Boston 8th to 12th of November 2019.

SIXTH NATIONAL MICROBIOTA CONFERENCE

The annual National Microbiota Conference on the 19th of November 2019, was again co-hosted by NoPSC Group Leader Johannes R. Hov. This year the tittle was "Fecal Microbiota Transplantation". Keynote speaker was Dr. Christian Lodberg Hvas from University of Aarhus, Denmark. Here Beate Vestad, PhD student in the Genomics and Metagenomics group of NoPSC, recieved the Tore Midtvedt's Prize for best abstract. (4)

NEW EMPLOYEES

Several new employees joined NoPSC in 2019: Post Doc Kathrine Sivertsen Åsrud, financed by Espen Melum's Young Researcher Talent funding, PhD student Guri Fossdal, financed by Health West funding, PhD student Mikal Jacob Hole, financed by Health South East funding and PhD student Tine Simensen Oldereid, also financed by Hearth South East.

SOCIAL MEET UPS

NoPSC employees also gather outside work. Among others happenings that included; Pay check meetup with Dart, Plant Bingo, Mushroom trip and a visit to the Norwegian Cancer Society's Science center in 2019. (5)

FUNDING FROM HORIZON 2020

The project "DYNAFLOW: Dynamic bile flow modeling and cellular sensing in primary sclerosing cholangitis" is in its last phase, still employing our engineer Lisa Løvold. This continues to stengthen key aspects of our research and the biobank collaborations with the Department of Pathology at Oslo University Hospital.

SOUTH-EAST REGIONAL HEALTH AUTHORITY

The Regional Health Autority South-Eastern Norway approved one application from NoPSC in 2019. The project was initiated by Johannes Hov and called "Precision-MAID: Microbial Precision Medicine assisted by Artificial Intelligence in inflammatory bowel Disease. It will finance one PhD student starting in 2020.

WEST REGIONAL HEALTH AUTHORITY

In 2019 we also got funding from the Norwegian West Health Authority for the project; Surrogate markers of natural history, disease severity and prognosis in primary sclerosing cholangitis in a prospective, national cohort. This finances a PhD position in the NoPSC group in Bergen and the position is filled by MD Guri Fossdal.

Networks

KEY LOCAL COLLABORATORS

Research Institute for Internal Medicine (RIIM)
The Institute is headed by Prof. Bente Halvorsen and the research groups led by Espen Melum and Johannes E.R. Hov respectively are located at RIIM. Several collaborative projects are established with, among others, Prof. Pål Aukrust, Børre Fevang, Thor Ueland and Bente Halvorsen groups.

Department of Transplantation Medicine
Department Head, Prof. Pål-Dag Line, Dr. Einar Martin Aandahl and Dr. Bjarte Fosby collaborate with NoPSC on projects related to liver transplantation in PSC and induced murine models of cholangitis.

Department of Rheumatology, Dermatology and Infectious diseases
Assoc. Prof. Marius Trøseid is a key collaborator for NoPSC on microbiome studies. Rheumatologists Prof. Øyvind Molberg and post doc Anna-Maria Hoffmann-Vold also collaborate on immunology and microbiome studies.

Department of Pathology
Dr. Peter Jebsen, Prof. Tor J. Eide, Dr. Henrik Reims and Dr. Krzysztof Grzyb are involved in the histological and immunohistochemical evaluation of tissue samples from PSC patients and samples from experimental mouse models.
Prof. Frode Jahnsen is a collaborator on microbiome studies.

Department of Gastroenterology (Ullevål)
Prof. Bjørn Moum, department head Asle Medhus and post doc Marte Lie Høivik are important collaborators on multiple projects including the original IBSEN and the new IBSEN III study.

Department of Cardiology
Prof. Lars Gullestad is an important collaborator on microbiome of statins and cardiovascular disease.

Center for clinical heart research
Prof. Ingebjørg Seljeflot is a collaborator on circulating biomarkers of the gut barrier.

Department of infectious diseases
Post doc Dag-Henrik Reikvam is another key collaborator on gut microbiome studies.

Department of Medical Genetics
The Immunogenetics group, led by Prof. Benedicte A. Lie is involved in several projects related to the further characterization of the HLA association in PSC. The Norwegian Sequencing Center hosts the NoPSC MiSeq next generation sequencing machine.

Institute of Immunology
NoPSC has a longstanding collaboration with the Institute of Immunology in our functional genetic projects. In particular, the good collaborations with Section of Transplantation Immunology, led by Prof. Torstein Egeland and Prof. John Torgils Vaage, and the research group of Fridtjof Lund-Johansen, are important in the activities of NoPSC.

Department of Medical Biochemistry
In conjunction with the establishment of the NoPSC Biobank quality control Project the collaboration with Dr. Yngve Thomas Bliksrud is highly appreciated.

Institute for Cancer Research
A collaboration with Prof. Ragnhild Lothe and Prof. Guro Lind at the Department of Molecular Oncology, OUS Radiumhospitalet is the basis for epigenetics-centered projects on early diagnosis of cholangiocarcinoma in PSC.

Department of Radiology
The involvement of the Department of Radiology at OUS Rikshospitalet in the prospective follow-up of PSC patients has been crucial for the success of the initiative. We are particularly grateful to Dr. Andreas Abildgaard, Dr. Knut Brabrand, Vanja Cengija and Gunter Kemmerich for their active contributions.

KEY NATIONAL COLLABORATORS

The IBSEN study group
The biological material collected by Prof. Morten Vatn, Prof. Bjørn Moum and several other co-workers of the IBSEN study group is still important for several of the basic genetic and metagenomic studies at NoPSC.

Akershus University Hospital
The collaboration with Dr. Kristin Kaasen Jørgensen regarding the regional network for Autoimmune Liver Diseases is ongoing and will continue for many years to come. Prof Jørgen Jahnsen's group at Department of Gastroenterology and Dr. Anne Nergård and Dr. Aida Kapic Lunder at the Department of Radiology are important contributors and collaborators in MRI studies in the IBSEN study and the new IBSEN III study.

Haukeland University Hospital and University of Bergen
For the prospective PSC cohort and advanced imaging modalities there is a close collaboration with Prof. Odd Helge Gilja and several other researchers at the Section for Gastroenterology and the Norwegian Centre of Excellence in Gastrointestinal Ultrasonography at the Medical Department at Haukeland University Hospital in Bergen. For the bile acid and microbiota projects, Prof. Rolf Berge at the University of Bergen provides the serum lipid measurements.

Haraldsplass Deaconess Hospital
Our leader for the clinical group in Bergen, Dr. Mette Vesterhus, holds a permanent position at Haraldsplass Deaconess Hospital, hence we have a strong collaboration there too.

KEY INTERNATIONAL COLLABORATORS

Karolinska University Hospital, Stockholm, Sweden
Prof. Annika Bergquist is a close collaborator on clinical projects in PSC and has also participated in the genetics studies. Associate Prof. Niklas Björkström (now our guest professor) is involved in projects relating to human immunology in PSC.

Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden
Fredrik Bäckhed and Hanns-Ulrich Marschall have been collaborators related to the gut microbiota axis for several years. Bäckhed (guest professor at NoPSC from 2012 till 2015) is an expert on gut microbiota, metabolism and gnotobiotic animals and has been an advisor and collaborator on gut microbiota studies in mice, while hepatologist Hanns-Ulrich Marschall contributes with bile acids expertise.

Institute for Clinical and Molecular Biology Christian-Albrechts University, Kiel, Germany
Prof. Stefan Schreiber and Prof. Andre Franke's groups in the German excellence cluster "Inflammation at interfaces" are involved in technically advanced studies within the genetic and metagenomic projects. Prof. In addition, Prof. John Baines (joint position at Christian-Albrechts University and the Max Planck Institute of Evolutionary Biology in Plön) are an important collaborator in the metagenomic projects.

Nordic BioScience, Denmark
Morten Karsdal, CEO of Nordic Biosciences in Denmark, has focused his research on the discovery and development of novel biochemical markers of fibrosis, and collaborates with NoPSC on several projects related to the characterization of fibrosis and the development of novel, targeted, PSC-specific fibrosis markers as prognostic tools in PSC.

The Nordic Liver Transplant Group
Collaborators in Helsinki (Dr. Arne Nordin and Prof. Helena Isoniemi), Stockholm (Prof. Bo-Göran Ericzon), Gothenburg (Prof. William Bennet) and Copenhagen (Dr. Allan Rasmussen) are involved in several projects where data from the Nordic Liver Transplant Registry are required.

Universitätsklinikum Dresden, Germany
There is a growing collaborative activity with Prof. Jochen Hampe and Prof. Sebastian Zeissig. With Prof. Hampe we collaborate within the framework of the Horizon2020 program; Dynaflow. Prof. Zeissig is participating in the NKT-related projects that are being performed in the Experimental Group.

Institute of Pathology, University Hospital Heidelberg, Germany
Prof. Peter Schirmacher, Head of Pathology at the University Hospital Heidelberg in Germany, represents a world-leading center expert in hepato-biliary pathology. Together with post.doc Benjamin Goeppert he provides pathology expertise to collaborational projects related to genomic profiling of PSC-associated biliary tract cancers.

Department of Internal Medicine I, University of Bonn, Germany
Dr. Tobias J. Weismüller is leading the International PSC Study Group (IPSCSG) database project comprising more than 8000 PSC patients and is an important collaborator within the IPSCSG.

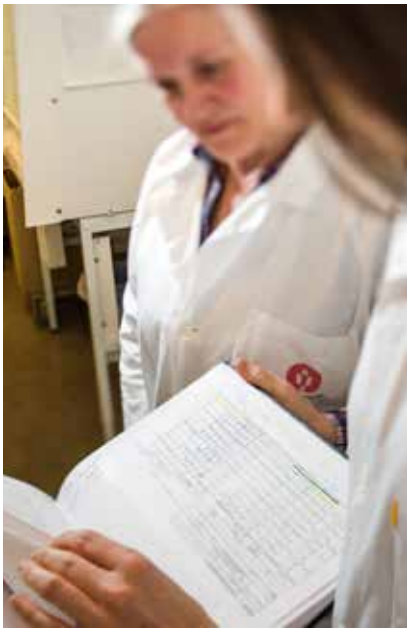
Netherlands, IPSCSG
The Internationsl PSC Study Group, IPSCSG, is in Amsterdam, in the capable hands of Prof. Cyriel Ponsioen and Prof. Ullrich Beuers at the University of Amsterdam's Faculty of Medicine.

Cambridge Institute for Medical Research, UK
The HLA association in PSC poses particular challenges, and the collaboration with Prof. John Trowsdale and senior researcher James Traherne and Vasilis Kosmoliaptsis in Cambridge is invaluable for the progress of several of our functional genetic projects.

Dept of Medicine, Univerity of Cambridge, Addenbrookes's Hospital, UK
Prof. Arthur Kaser (former Guest Professor at NoPSC), Head of the Division of Gastroenterology and Hepatology at Addenbrooke's Hospital, Cambridge, UK, is still involved in one of the main translational work packages related to the functional characterization of one of the PSC risk genes; GPR35. This project was funded within the Scientia Fellows' program of the University of Oslo through 2018 and involved post.doc. Georg Schneditz and his supervisor Dr. Nicole Kaneider-Kaser.

University of Birmingham, UK
Prof. David Adams (former Guest Professor at NoPSC) at the Center for Liver Research at the Institute of Biomedical Research, University of Birmingham, collaborate on several projects related to the further characterization of the HLA related immune response in PSC. Post.doc. and Scientia Fellow Brian Chung participates actively in these projects from Oslo.

Royal Free Hospital London, UK
Prof. Massimo Pinzani (currently one of our Guest Professors), director of the UCL Institute for Liver and Digestive Health at UCL and the Royal Free Hospital in London, and Dr. Douglas Thorburn at the same institutions, collaborate with NoPSC on projects related to the characterization of fibrosis and the development of novel, targeted, PSC-specific fibrosis markers as prognostic tools in PSC in a tri-party collaboration with Nordic Biosciences.



Medical University of Vienna and Medical University of Graz, Austria
In collaboration with Prof Michael Trauner and Prof. Peter Fickert, ongoing projects aim at crossvalidating findings in mouse models of PSC with human data. Prof. Michael Trauner Guest Professor at NoPSC through 2018 has extensive experience in animal models of PSC and serves as an important collaborator related to the development of a bile duct specific Cre mouse.

Sapienza, Università di Roma, Italy
Prof. Eugenio Gaudio, Domenico Alvaro and coworkers are experts on biliary tree stemcells, and material from the NoPSC Biobank is used to explore these cells in PSC patients. In addition we have a close collaboration with the COST-action European Cholangiocarcinoma Network where Prof. Vincenzo Cardinale serves as action chair.

Biodonostia Research Institute, Donostia University Hospital, San Sebastian, Spain
Dr. Jesus M. Banales is the Head of the Liver Diseases Group at the Biodonostia Research Institute and the coordinator of European Network for the study of Cholangiocarcinoma, and serves as an important collaborator on projects related to PSC-associated biliary tract cancers.

Toronto Centre for Liver Disease, Toronto General Hospital, Canada
Dr. Gideon Hirschfield (former Birmingham, UK) continues the collaboration with NoPSC regarding characterization of the HLA related immune response in PSC from his workplace at Toronto Centre for Liver Disease. Biostatistician Bettina E. Hansen is leading the statistical analyses of clinical data collected in the International PSC Study Group (IPSCSG) database project, assisted by Dr. Aliya Gulamhusein at the same institution.

The Mayo Clinic, Rochester, USA
Collaboration with Dr. Konstantinos Lazaridis and Dr. Lewis Roberts at the Mayo Clinic in Rochester has been ongoing regarding our projects on the genetics of PSC. Via infrastructure at the Mayo Clinic, DNA from PSC patients in USA and Canada are collected and utilized in local projects as well as for verification of findings in genetic studies at NoPSC.

Brigham and Women's Hospital, Harvard Medical School, Boston, USA
Prof. Richard Blumberg is an important collaborator in Dr. Espen Melum's projects related to NKT cells.

Publications 2019

HIGHLIGHTED PUBLICATIONS

*__Schneditz G__, Elias JE, Pagano E, Zaeem Cader M, Saveljeva S, Long K, Mukhopadhyay S, Arasteh M, Lawley TD, Dougan G, Bassett A, __Karlsen TH__, Kaser A, Kaneider NC (2019) **GPR35 promotes glycolysis, proliferation, and oncogenic signaling by engaging with the sodium potassium pump,** Sci Signal, 12 (562)

Genetic studies of Primary sclerosing cholangitis (PSC) have been highly successful in identifying disease-associated single-nucleotide polymorphisms (SNPs), but elucidating the biology responsible for these associations has proven to be a challenge. Polymorphisms in the G protein–coupled receptor 35 (GPR35) are associated with risk for PSC and ulcerative colitis (UC) across multiple ethnicities. GPR35 is a member of a large family of receptors, for which small-molecule therapeutics have been most successfully developed. The endogenous ligands for GPR35 remain however unidentified or disputed, and the basic biological function of the receptor unknown. GPR35 is expressed in a tissue-specific pattern, with high expression in myeloid and intestinal epithelial cells. These cell types are implicated in both UC and PSC pathogenesis and associated cancer. Both diseases carry a high risk of inflammation-associated cancer, often incurable, with an urgent need for new treatment options.

We discovered that GPR35 promotes the activity of the sodium potassium pump (Na/K-ATPase), a ubiquitous and essential transmembrane pump that sets the membrane potential in cells. The PSC-associated variant of GPR35 induced a more pronounced increase in Na/K-ATPase activity. This stimulation of Na/K-ATPase activity enhanced glycolytic metabolism in both macrophages and epithelial cells. As a consequence, proliferation in intestinal epithelial cells in particular was significantly increased. We furthermore showed mechanistically how the hypermorphic mutation may alter the risk for developing UC and PSC and how GPR35 may contribute directly to the cancer risk associated with these diseases. Ultimately, we developed a synthetic inhibitor targeting Gpr35 that decreased tumor burden in mouse models of intestinal cancer. This could represent a targeted therapeutic for patients at high risk for cancer such as in UC and PSC.

*__Melum E__, __Jiang X__, Baker KD, Macedo MF, Fritsch J, Dowds CM, Wang J, Pharo A, Kaser A, Tan C, Pereira CS, Kelly SL, Duan J, __Karlsen TH__, Exley MA, Schütze S, Zajonc DM, Merrill AH, Schuchman EH, Zeissig S, Blumberg RS (2019) **Control of CD1d-restricted antigen presentation and inflammation by sphingomyelin,** Nat Immunol, 20 (12), 1644-1655

Natural killer T (NKT) cells are common immune cells in the liver. NKT cells are activated by lipids and this article describes how a lipid, called sphingomyelin, which is a common component of cell membranes, can regulate the development of NKT cells and the NKT response in various NKT driven disease models. To investigate this, material from patients and mice were used. We demonstrate that sphingomyelin blocks the development of NKT cells in a mouse model and how the same mechanisms are also present in humans. Furthermore, we show the molecular interaction of sphingomyelin with CD1d, which is the molecule that presents lipids to NKT cells. Mice that were treated with an enzyme that breaks down sphingomyelin and mice receiving bone marrow transplantation exhibited restoration of NKT cells. Both of these approaches show the importance of sphingomyelin in the hematopoietic system.
The findings of the article show important mechanisms related to the function of NKT cells, and are also important for patients with Niemann-Pick's disease (a rare disease with accumulation of sphingomyelin) and diseases where NKT cells are of importance in the pathogenesis.

*__Dhillon AK__, Kremer AE, __Kummen M__, __Boberg KM__, Elferink RPO, __Karlsen TH__, Beuers U, __Vesterhus M__, __Hov JR__ (2019) **Autotaxin activity predicts transplant-free survival in primary sclerosing cholangitis,** Sci Rep, 9 (1), 8450

In the study "Autotaxin activity predicts transplant-free survival in primary sclerosing cholangitis" , Dhillon et al. investigated the potential role of autotaxin as a biomarker in PSC. The main finding was that higher autotaxin levels

in blood were associated with more severe disease, as measured by shorter time to liver transplantation or death. Autotaxin is an enzyme that produces a particular type of lipid that in patients with PSC, and other cholestatic liver diseases, has been linked to itching, an important clinical problem. This may suggest that itching is not only a symptom of obstructed bile ducts, but could also be related to the underlying disease process. The study is a typical example of the biomarker studies performed at NoPSC, and shows how biomarkers may be relevant as clinical tools to define disease or predict its outcome, but also to shed light on mechanisms of disease.

Liwinski T, Zenouzi R, John C, Ehlken H, Rühlemann MC, Bang C, Groth S, Lieb W, Kantowski M, Andersen N, Schachschal G, **Karlsen TH**, **Hov JR**, Rösch T, Lohse AW, Heeren J, Franke A, Schramm C (2019)
Alterations of the bile microbiome in primary sclerosing cholangitis, Gut; 69(4), 665-672.

In addition to serving as the basis of our own research, the NoPSC biobank of liver and biliary diseases provides material for multiple international research projects in collaboration with other groups. One typical example is the 2019 study "Alterations of the Bile Microbiome in Primary Sclerosing Cholangitis" by Liwinsky et al.. The study was driven by collaborators in Hamburg and Kiel, and NoPSC contributed with bile samples from PSC patients collected during endoscopic examinations of the bile ducts. The study finds that PSC patients have a different composition of bacteria in bile than patients without PSC. The altered bacterial composition was associated with the composition of bile acids in the bile fluid which could hypothesized to influence the disease.

ADDITIONAL RESEARCH ARTICLES
Primary articles marked with an asterix

Rühlemann MC, Solovjeva MEL, Zenouzi R, Liwinski T, **Kummen M**, Lieb W, **Hov JR**, Schramm C, Franke A, Bang C (2019)
Gut mycobiome of primary sclerosing cholangitis patients is characterised by an increase of *Trichocladium griseum* and *Candida* species
Gut (in press)

Rühlemann M, Liwinski T, Heinsen FA, Bang C, Zenouzi R, **Kummen M**, Thingholm L, Tempel M, Lieb W, **Karlsen T**, Lohse A, **Hov J**, Denk G, Lammert F, Krawczyk M, Schramm C, Franke A (2019)
Consistent alterations in faecal microbiomes of patients with primary sclerosing cholangitis independent of associated colitis
Aliment Pharmacol Ther, 50 (5), 580-589

Saffioti F, Roccarina D, **Vesterhus M**, **Hov JR**, Rosenberg W, Pinzani M, Pereira SP, **Boberg KM**, Thorburn D (2019)
Cholangiocarcinoma is associated with a raised enhanced liver fibrosis score independent of primary sclerosing cholangitis
Eur J Clin Invest, 49 (5), e1308

*__Storm-Larsen C__, Myhr KM, Farbu E, Midgard R, Nyquist K, Broch L, Berg-Hansen P, Buness A, Holm K, Ueland T, Fallang LE, Burum-Auensen E, **Hov JR**, Holmøy T (2019)
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Mult Scler J Exp Transl Clin, 5 (4), 1-13

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Complexity in unclassified auto-inflammatory disease: a case report illustrating the potential for disease arising from the allelic burden of multiple variants
Pediatr Rheumatol Online J, 17 (1), 70

Thingholm LB, Rühlemann MC, Koch M, Fuqua B, Laucke G, Boehm R, Bang C, Franzosa EA, Hübenthal M, Rahnavard A, Frost F, Lloyd-Price J, Schirmer M, Lusis AJ, Vulpe CD, Lerch MM, Homuth G, Kacprowski T, Schmidt CO, Nöthlings U, **Karlsen TH**, Lieb W, Laudes M, Franke A, Huttenhower C (2019)
Obese Individuals with and without Type 2 Diabetes Show Different Gut Microbial Functional Capacity and Composition
Cell Host Microbe, 26 (2), 252-264.e10

Trøseid M, Mayerhofer CCK, Broch K, Arora S, Svardal A, **Hov JR**, Andreassen AK, Gude E, Karason K, Dellgren G, Berge RK, Gullestad L, Aukrust P, Ueland T (2019)
The carnitine-butyrobetaine-TMAO pathway after cardiac transplant: Impact on cardiac allograft vasculopathy and acute rejection
J Heart Lung Transplant, 38 (10), 1097-1103
Mazzawi T, Hausken T, **Hov JR**, Valeur J, Sangnes DA, El-Salhy M, Gilja OH, Hatlebakk JG, Lied GA (2019)
Clinical response to fecal microbiota transplantation in patients with diarrhea-predominant irritable bowel syndrome is associated with normalization of fecal microbiota composition and short-chain fatty acid levels
Scand J Gastroenterol, 54 (6), 690-699

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Isolation and propagation of primary human cholangiocyte organoids for the generation of bioengineered biliary tissue
Nat Protoc, 14 (6), 1884-1925

*Mjelle AB, Mulabecirovic A, Havre RF, Rosendahl K, Juliusson PB, Olafsdottir E, Gilja OH, **Vesterhus M** (2019)
Normal Liver Stiffness Values in Children: A Comparison of Three Different Elastography Methods
J Pediatr Gastroenterol Nutr, 68 (5), 706-712

Lunder AK, Bakstad LT, Jahnsen J, Borthne A, **Hov JR**, Vatn M, Negård A (2019)
Assessment of Bowel Inflammation and Strictures by Magnetic Resonance Enterography in Long-term Crohn's Disease
J Crohns Colitis, 13 (5), 607-614

*Jørgensen SF, **Holm K**, Macpherson ME, **Storm-Larsen C**, **Kummen M**, Fevang B, Aukrust P, **Hov JR** (2019)
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Tschuor C, Ferrarese A, Kuemmerli C, Dutkowski P, Burra P, Clavien PA; Liver Allocation Study Group; Lendoire J, Imventarza O, Crawford M, Andraus W, D'Albuquerque LAC, Hernandez-Alejandro R, Dokus MK, Tomiyama K, Zheng S, Echeverri GJ, Taimr P, Fronek J, de Rosner-van Rosmalen M, Vogelaar S, Lesurtel M, Mabrut JY, Nagral S, Kakaei F, Malek-Hosseini SA, Egawa H, Contreras A, Czerwinski J, Danek T, Pinto-Marques H, Gautier SV, Monakhov A, **Melum E**, Ericzon BG, Kang KJ, Kim MS, Sanchez-Velazquez P, Oberkofler CE, Müllhaupt B, Linecker M, Eshmuminov D, Grochola LF, Song Z, Kambakamba P, Chen CL, Haberal M, Yilmaz S, Rowe IAC, Kron P (2019)
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J Hepatol. 71 (4), 707-718

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Pathogenesis, diagnosis and treatment of premalignant and malignant stages of cholangiocarcinoma in primary sclerosing cholangitis
Liver Int, 39 (12), 2230-2237

Kummen M, **Hov JR** (2019)
The gut microbial influence on cholestatic liver disease
Liver Int, 39 (7), 1186-1196

Banales JM, Huebert RC, **Karlsen T**, Strazzabosco M, LaRusso NF, Gores GJ (2019)
Cholangiocyte pathobiolo
Nat Rev Gastroenterol Hepatol. 16 (5), 269-281.

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J Hepatol, 71 (1), 5-8

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BMC Emerg Med, 19 (1), 55

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Enzymatic Digestion of Hyaluronan-Based Brain Extracellular Matrix *in vivo* Can Induce Seizures in Neonatal Mice
Front Neurosci, 13, 1033

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